REMARKS

Applicant respectfully requests reconsideration of the present application in view of the reasons that follow.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

The Examiner rejects claims 25-34 under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the enablement requirement. This rejection is respectfully traversed.

The present invention provides a method of identifying a developmentally competent nuclear donor cell line. The method involves separating cells from a cell line and performing nuclear transfer procedures to make nuclear transfer embryos of the cell lines. The developmental competence of each of the embryos can then be determined by comparing a plurality of nucleic acid molecules obtained from the embryos to a gene expression database. Using such a comparison one is able to identify those embryos resulting from the nuclear transfer of a developmentally competent nuclear donor. The methods identify one or more expression events that occur within cells, tissues, embryos, and/or animals that correlate to developmental competence. The present invention therefore enables producers of cloned mammals to eliminate embryos that will ultimately fail. This can be done early in the production process, thereby enabling the user to save resources that would otherwise be expended on embryos that will ultimately fail to produce a viable mammal.

The Examiner asserts that the specification allegedly fails to enable the claims because it fails to provide the sequences of the genes of the database that are characteristic and indicative of developmental competence. But this concern is misplaced, since the exact genes or sequences involved will depend on the specific cell lines used or genes selected, and the precise sequences of any individual application of the method are not essential to the invention. What is important is to identify sequences for the database that are known to be present and/or expressed in a cell

line that has been demonstrated to be developmentally competent, but that are present and/or expressed at a reduced or nondetectable level in cell lines that are developmentally incompetent (specification, p. 17, lines 24-29), i.e., ESTs that are differentially expressed. Therefore, the methods are more broadly applicable than to single and precise gene sequences.

The specification provides copious instruction on how to identify differentially expressed nucleic acids (p. 50, line 12). The specification also provides 4 examples of published U.S. patents that describe such techniques (p. 50, line 20 – p. 51, line 1). Various techniques are also described in the specification for correlating the expression patterns of tissue-specific and developmentally-specific marker molecules, which can be correlated to characteristics such as developmental competence or incompetence. These individual techniques are also well known to the skilled artisan. For example, Pearson correlation, hierarchical clustering, Euclidian distinct analysis, and neighbor analysis can be used to predict which marker molecules are most closely related to a given characteristic (specification, page 52, lines 1-4). Example 7 provides detailed instructions on one method of differential display of RNAs from in vivo, in vitro, and nuclear transfer-derived embryos (see also p. 52, line 19 *et seq.*), and Example 8 provides similar detailed information on building a cDNA library of embryonic germ cells. And Examples 10-12 provide information of the use of macroarrays and microarrays, and the identification of developmentally competent or incompetent cell lines.

Furthermore, the Figures illustrate the types of data that are gathered in these analyses. Figure 4 describes the comparison of banding patterns generated by differential display between five individual day 7 in vivo embryos, six individual day 5 IVF embryos, and 5 individual embryos reconstructed by NT using a developmentally incompetent cell line. As is apparent from the data, investigators often do not know (and do not need to know) the precise sequences. Rather, they need only compare sequences using these established techniques and correlate sequences to developmental competence or incompetence.

Therefore, as is apparent from consideration of the full disclosure, the person of ordinary skill is readily able to work the invention.

The Examiner also alleges that the claims encompass comparison of expression profiles that have not been appropriately matched for variables that will affect the profiles such as species, developmental stage, and culture conditions (Office Action mailed 10/6/03, p. 5). Again, this concern is respectfully submitted to be misplaced, because the recited methods can be used with any clonable mammalian species as such comparisons are valid across species. The developmental stage of the cells is irrelevant since cells at any stage will carry the same genes, which can be compared according to the recited methods. Nor will the culture conditions affect the gene comparison as any reasonable conditions known to the person of ordinary skill in the art are useable. This is because the method utilizes a statistical comparison of the frequency of occurrence of individual genes. The task of this analysis is made far more manageable by the use of gene expression analysis.

Therefore, it is respectfully submitted that an emphasis on specific sequences or conditions is misplaced. The present inventors have invented a method of identifying developmentally competent nuclear donor cell lines that utilizes a molecular approach to identifying sequences associated with developmental success. The method compares those sequences between individual embryos against a gene expression library and correlates gene markers present with developmental competence. The methods have broad applicability, as will be recognized by the person of ordinary skill. Accordingly, the present claims are not overly broad in view of the broad applicability of the methods.

The Examiner rejects claims 25-34 under 35 U.S.C. 102(b) as allegedly being anticipated by De Sousa (1999, Cloning, Vol. 1, pp. 63-69). This rejection is respectfully traversed.

To anticipate a claim, it is necessary that the cited reference disclose each and every element as set forth in the claim, either inherently or expressly *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 632; 2 USPQ2d 1051,1053 (Fed. Cir. 1987); MPEP 2131.

The present claims recite, among other requirements, that the developmental competence of recited nuclear transfer embryos is determined by comparison of nucleic acid molecules from

nuclear transfer embryos to a gene expression database. The claims require that comparison to the gene expression database is probative of the developmental competence of the embryo. De Sousa completely fails to disclose or suggest that the developmental competence of nuclear transfer embryos can be determined by comparing nucleic acids derived from the embryos to a gene expression database.

The disclosure of De Sousa examined only the conservation of mRNA expression in a single cell type (fibroblasts). De Sousa discloses a comparison of mRNAs from fetal fibroblast NT embryos with those of NT embryos reconstructed from embryonic blastomeres (abstract, Fig. 1). De Sousa found that the mRNA profile from all blastocyst types is highly conserved and distinct from fetal fibroblast cells, with approximately 95% conservation between fetal fibroblast NT embryos, NT embryos reconstructed from embryonic blastomeres, and in vivo blastocysts, when compared with in vitro derived blastocysts (p. 66, right column).

Furthermore, De Sousa utilized pooled embryos (p. 65, left column, 2nd paragraph), which would have made it difficult or impossible to detect genetic variation to an extent necessary to correlate developmental competence with comparison to a gene expression database. For example, if one embryo had a very high production of a particular gene, and another embryo had a very low production of the same gene, in a pooled assay such as that disclosed by De Sousa, this difference would be averaged out making it likely that important genetic differences would be overlooked. It is not surprising that De Sousa used pooled embryos, because his objective and disclosure are not directed towards identifying genetic markers and correlating them with developmental competence.

But De Sousa never discloses or suggests that the developmental competence of nuclear transfer embryos can be determined by comparing nucleic acids derived from the embryos to a gene expression database, as presently claimed. For all of these reasons, the presently claimed invention is not anticipated by De Sousa.

Closing

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date March 8, 2004 By _____

Richard J. Warburg
FOLEY & LARDNER LLP
Customer Number: 30542
Telephone: (858) 847-6700
Facsimile: (858) 792-6773

Richard San Pietro
Attorney for Applicant
Registration No. 45,071